REMARKS

Applicants acknowledge with appreciation the courtesy of the interview extended to the inventors and the undersigned attorney on January 17, 2007, by the Examiner in charge of this application, Examiner Cook, and her supervisor, Mr. Long Lee, at which time the outstanding rejections were discussed as well as the distinguishing features of the claimed invention over the prior art. A schematic representation of the present invention was presented and the importance of the separation and measurements steps in the present invention were emphasized.

Modified claims were presented at the interview in an effort to clarify the distinguishing features of the presently claimed invention from the prior art. These claims are included in the present amendments to the claims. Claim 76 corresponds to claim 50 as discussed at the interview. Claim 77 corresponds to previous claim 53, claim 78 to previous claim 54; 79 to 58, 80 to 59, 81 to 61, and 82 to 90 correspond to previous claims 62 to 70. Finally, claims 73 to 75 have been canceled from the application without prejudice or disclaimer. Claims 51, 52, and 60 were canceled without prejudice or disclaimer. The claims now remaining in the application are claims 76 - 90. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 USC 112 and are clearly patentable over the references of record.

Applicants noted at the interview that the presently claimed invention is patentably distinct from the claimed subject matter in the related copending application over which the provisional obviousness type double patenting rejection has been issued. As noted in the Examiner interview summary, the present claims include the isolation of the holo forms of TC-II and HC whereas the claims of the related application do not rely on this separation which is not an obvious modification of the copending claims. Moreover, the claims in the related application will be further amended to clarify

the distinctions from the presently claimed invention. Accordingly, this rejection should be withdrawn.

In any case, and in accordance with accepted USPTO procedure, it is understood that the provisional obviousness double patenting rejection is held in abeyance until one of the applications is allowed at which time one application will be allowed and the other subject to a non-provisional obviousness type double patenting rejection, if the rejection is not withdrawn.

The rejection of claims 50-54, 58-70 and 73-75 under 35 USC 112, first paragraph, has been carefully considered but is most respectfully traversed in view of the further amendments to the claims and the following comments. The presently claimed invention includes the separation step utilizing cobalamin or an analogue or fragment thereof which selectively binds the apo-forms of TCII and haptocorrin (HC) in the sample. The specification clearly defines and enables cobalamin, as recognized in the Official action, as it does with respect to analogue which is shown as biotinylated cobalamin. Moreover, the claimed fragment is not any fragment as stated on page 5 of the Official Action, but as specified in the claim, a fragment which selectively binds the apo-forms of TCII and HC as discussed at the interview. It is believed that the Examiner agreed, at the interview, that the term as defined in the claims is acceptable and therefore, it is most respectfully requested that this rejection be withdrawn.

It is noted that the amended claims now present in the application parallel the rejected claims 50-52, 65-68, and 71 under 35 USC 103(a), as being obvious over Herbert in view of J. Van Kapel et al and further in view of Frater-Schroeder (newly cited). Applicants most respectfully submit that the claims as now amended make the distinction of the claimed subject matter over the prior art more evident. However, the Examiner correctly noted that Applicants' previous arguments were persuasive, at the bottom of page 12, of the outstanding Official Action. The Frater-Schroeder reference added to the previous rejection does not overcome the deficiencies of the primary

references in the previous rejection as the added reference does not teach the initial separation step as clearly set forth in the claims.

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

Applicants most respectfully submit that the Summary (copy enclosed) presented at the interview clearly points out some of the differences between the presently claimed invention and the primary reference to Herbert. As noted in the Summary, Herbert isolates the TCII (apo and holo) while the presently claimed invention isolates

the holo-forms (the holoTCII and the holo-HC). This is followed by a measurement. This is clearly set forth in new claim 76 which claims an assay method for the determination of holo-Transcobalamin II (holo-TCII) in a body fluid sample, comprising:

contacting a sample of a body fluid with an immobilized or immobilizable cobalamin or an analogue or fragment thereof **which selectively binds the apo-forms of TCII and haptocorrin (HC) in said sample over the holo-forms thereof**,

separating said selectively bound TCII from said sample or rendering said selectively bound TCII unable to bind to a specific binding ligand for TCII or holo-TCII,

contacting the non-bound TCII with a specific binding ligand for TCII or holo-TCII to bind said holo-TCII to form a ligand bound fraction and a non-ligand bound fraction, which is followed by a measuring step for TCII.

On the contrary, Herbert does not have this separation step and Herbert measures cobalamin liberated from TCII (Holo HC was removed in the separation step). The presently claimed invention measures the TCII protein (only holo TcII remains after the separation, the apo TCII was removed. These are quite different as would be appreciated by one of ordinary skill in the art.

Specifically, none of the prior art cited carries out a measurement of the TCII **protein** component of a holo-TCII containing sample, whereby to assess the holo-TCII content. This step is important in the context of the complete assay because it is only in combination with the apo-binding pre-treatment step of the presently claimed invention that assessment of the TCII component can provide a measure of holo-TCII in the originating sample. Thus, **the combination of apo-prebinding and assessment of TCII content gives a new and simpler approach to holo-TCII measurement which is not suggested by the prior art**.

As noted at the interview and in the attached summary, the advantage of measuring the holo TCII protein as in the presently claimed invention makes it possible to use the more robust and sensitive sandwich immunoassay. Measuring the

cobalamin liberated from Holo TC (Herbert) can only be achieved with less robust and sensitive competitive assays.

Applicants most respectfully submit that no cited document provides a method for holo-TCII assessment comprising a pre-binding step to remove apo-TCII (see below) and no cited document utilizes measurement of the TCII protein to represent the holo-TCII level in the sample. This latter shortcoming in probability arises from the fact that without an apo-prebinding step, measurement of TCII levels does not provide any information on holo-TCII content. Among the contributions of the present inventors is the realization that by incorporating an apo-prebinding step into a holo-TCII assay, measurement of the remaining TCII content will represent the original holo-TCII level.

In view of the above, the Examiner's rejections on the grounds of obviousness should be withdrawn since no reference cited teaches or suggests, alone or in combination, the measurement of the TCII protein component in an assay for holo-TCII, and most significantly, no reference indicates the advantageous combination of pre-treatment to remove (or render non-reactive) the apo-TCII component, followed by measurement of the remaining TCII in the sample in accordance with the presently claimed invention. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

The Examiner has considered the Applicant's previous submissions with regard to lack of teaching of an apo-TCII pre-binding step, and indicates that these arguments were persuasive as stated in the paragraph bridging pages 12 and 13 of the Office Action.

As noted in the previous response, Applicants again most respectfully wish to point out that in order for the presence of a step relating to the pre-binding of apo-TCII to be obvious, the prior art should teach not only that binding of apo-TCII is known, but

further that there is some motivation by which a skilled artisan would derive an incentive to combine this with the teaching of a compatible holo-TCII assay, so as to provide the currently claimed method.

In the present case, Van Kapel provides for no selective binding of apo-TCII over holo-TCII. The method of Van Kapel simply attempts to allow both the apo-TCII and holo-TCII fractions to be measured. In this method, all of the TCII is bound to heparin. If the cobalamin bound to the heparin is released from, these beads and measured then the holo-TCII content may allegedly be determined, where as binding of further cobalamin onto the beads is reported to indicate the apo-TCII component. No selective binding of apo TCII is taught, and if the method of Van Kapel were effective then none would be needed. As a result, no teaching towards such a step can be provided by this reference. It is essential to distinguish separate *measurement*, of apo TCII and holo TCII, which is allegedly provided by Van Kapel but is not claimed in the present application, from specific *binding* of apo TCII but not holo TCII, which is presently claimed but not provided by Van Kapel.

Applicants most respectfully submit that the teaching of an apo-separation step as a tool to simplify a holo-TCII assay method is the essential starting point if a holo-TCII assay method comprising such a step is to be obvious. Applicants most respectfully submit that no such teaching can be found in any document known to date and as previously noted, Applicants' teaching may not be used to modify the prior art to arrive at the claimed subject matter.

Applicants further submit, as discussed at the interview, the Frater-Schroeder et al do not overcome the deficiencies of the primary reference and specifically traverse the statements in the Official Action in this regard. A complete copy of the reference is enclosed herewith for the convenience of the Examiner.

Applicants most respectfully submit that Frater-Schroeder et al describes a method to quantify total TC (apoTC + holoTC) by use of antibodies specific for human

TC. In essence, it is based on the same principle as the other two methods described in the references. The difference is that here antibodies specific for TC are used to isolate (and in this case quantify) total TC from total HC, whereas Herbert uses silica and van Kapel heparin for the same purpose. Frater-Schroeder et al also suggest that by subtracting the total TC value with a measured value for apoTC, the holoTC content can be estimated. ApoTC is only "removed" in a computational sense. No specific binding, and no physical separation of apoTC from holoTC is performed or suggested. Applicants most respectfully submit that it is likewise incorrect that Frater-Schroeder et al disclose a solid-phase immunoassay for cobalamin. Frater-Schroeder et al disclose a solid-phase immunoassay for total TC (apoTC + holoTC). The apoTC is then estimated by allowing it to bind radio-labeled cobalamin of known specific radioactivity, and the holoTC is computed as the difference between total TC and apoTC.

All three prior art references are based on the same principle (separating total TC from total HC). In contrast, the presently claimed invention uses a totally different principle (separating apoTC + apo HC from holoTC + holoHC). There is no teaching in any of the references towards this latter approach, and thus, even in hindsight the references cannot be combined in such a way as to provide the presently claimed method. Not one of the three cited articles teaches use of immobilized (or immobilizable) cobalamin (or analogs) for the purpose of physically separating apoTC from holoTC. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 62-64 and 75 under 35 USC 103(a) as being unpatentable over Herbert in view of Van Kapel et al. and further in view of Frater Schroeder for the reasons applied to claims 50-52, 65-68, 71, and 73-74 above and further in view of Hoyle et al has been carefully considered but is most respectfully traversed in view of the further amendments to the claims and above comments. The Hoyle et al reference does not overcome the deficiencies of the primary references for

the reasons discussed above. Accordingly it is most respectfully requested that this rejection be withdrawn.

More particularly, Applicants most respectfully submit that Hoyle et al discloses a method to measure cobalamin (vitamin B12) by allowing the cobalamin in the sample to compete with labeled cobalamin for a limited amount of a cobalamin binder, which in Hoyle et al is a monoclonal antibody to cobalamin. This assay principle, the competitive binding assay, was in general terms, first described by RP Ekins in 1960 (Clin Chim Acta 1960;6:453-9). The assay principle specifically used for free cobalamin was also well known at the time of Hoyle et al. It was for instance disclosed in the work of Victor Herbert and van Kapel, both public years before the work by Hoyle et al. The difference being that Victor Herbert and van Kapel used Intrinsic Factor as the cobalamin-specific binder whereas Hoyle et al used monoclonal antibodies.

The invention of Hoyle et al was that the use of monoclonal antibodies instead of Intrinsic Factor enabled a more exact determination of cobalamin because Intrinsic Factor (at that time) was available only in impure form (column 1 line 63 to column 2 line 9). The invention by Hoyle et al concerns only the final, quantitative step in the determination of holoTC, when the holoTC fraction has already been isolated and its cobalamin content released. Its principle is already disclosed in Victor Herbert and van Kapel. Applicants most respectfully submit that it has no relevance to either the assay principle of Herbert, van Kapel, and Frater-Schroeder et al or the principle of the presently claimed method. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 69 and 70 under 35 USC 103(a) as being unpatentable over Herbert in view of Van Kapel et al. and further in view of Frater-Schroeder for the reasons applied to claims 50-52, 65-68, 71, and 73-74 above and further in view of McLean et al has been carefully considered but is most respectfully traversed in view of the further amendments to the claims and above comments. The McLean et al

reference does not overcome the deficiencies of the primary references for the reasons discussed above. Accordingly it is most respectfully requested that this rejection be withdrawn.

More particularly, Applicants most respectfully submit that McLean et al use recombinant apoTC and holoTC only to assess the epitopes of their antibodies. The term "competition sandwich-enzyme-linked immunosrbent assay" refers to the competitive binding of monoclonal antibodies to apo- or holoTC. Different antibodies that compete for binding to apoTC or holoTC are defined as having the same epitope (i.e., the same binding sequence on the TC molecule).

As any person skilled in the art would know, the "assay" described by McLean et al has only a linguistic and no practical relationship to a quantitative competitive assay. The work by McLean et al cannot be combined with the other cited prior art because the subject matters are fundamentally different: quantitative measurement holoTC (Herbert, van Kapel, Frater-Schroeder) versus qualitative characterization of antibodies (McLean). Moreover, there is no argumentation put forward in either of the cited prior art references for why it would be advantageous to use holoTC instead of free cobalamin to construct the calibration curves. Therefore there would be no motivation to switch from the routinely (and solely) used cobalamin calibrators to the new and considerably more expensive holoTC calibrators. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 58-61under 35 USC 103(a) as being unpatentable over Herbert in view of Van Kapel et al. and further in view of Frater Schroeder for the reasons applied to claims 50-52, 65-68, 71, and 73-74 above and further in view of Hoyle et al has been carefully considered but is most respectfully traversed in view of the further amendments to the claims and above comments. The Hoyle et al reference does not overcome the deficiencies of the primary references for the reasons discussed above. Accordingly it is most respectfully requested that this rejection be withdrawn.

As indicated above, Applicants most respectfully submit that Hoyle et al discloses a method to measure cobalamin (vitamin B12) by allowing the cobalamin in the sample to compete with labeled cobalamin for a limited amount of a cobalamin binder and that the invention of Hoyle et al was that use of monoclonal antibodies instead of Intrinsic Factor enabled a more exact determination of cobalamin because Intrinsic Factor (at that time) was available only in impure form. Applicants most respectfully reiterate that this has no relevance to either the assay principle of Herbert, van Kapel and Frater-Schroeder et al or the principle of the presently claimed method. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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